## REMARKS

Applicants have cancelled Claims 22-24, 28 and 29 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Claims 25-27 and 35 are amended to delete elements (a) and (b). Claims 25-26 have been amended to delete the functional limitation, and to add the limitation that the nucleic acids hybridize to the complement of a nucleic acid of SEQ ID NO:1 under the specified stringent conditions. Claim 25 is amended to be in independent form, and Claims 26 and 38 are amended to depend from Claim 25. Claim 35 has been amended to delete the limitation added in the previous amendment, to include "or the complement thereof" after amended elements a-c, and to add the limitation that the claimed isolated nucleic acid be at least about 200 nucleotides in length. Claim 37 has been amended such that the claimed nucleic acid is at least about 250 nucleotides in length. New Claims 42-46 have been added.

Applicants submit that no new matter was added by the amendments, and that support for the amendments can be found throughout the specification. Support for the limitation added to claims 25-26 can be found, for example, on page 43, lines 21-30, and page 8, lines 11-14, and 27-33.

Support for the amendment to Claims 35 and 37, and new Claims 42-46 can be found, for example, on page 32, lines 4-15. Throughout the specification, the Applicants describe using the disclosed sequences to generate probes for use in conventional hybridization techniques such as Southern and Northern blotting, *in situ* hybridization, and PCR. (*See e.g.*, page 78, lines 30-33, and 83, lines 17-20). Those of skill in the art will recognize that such probes can be of various lengths. For example, the specification describes the use of fragments of a PRO polypeptide coding sequence as hybridization probes, and states that "[s]uch nucleic acid fragments are usually at least about 20 nucleotides in length...at least about 200 nucleotides in length...at least about 250 nucleotides in length...at least about 300 nucleotides in length...at least about 350 nucleotides in length...at least about 400 nucleotides in length...at least about 450 nucleotides in length...at least about 500 nucleotides in length..." etc. Combined, these disclosures clearly support the amendments to Claims 35 and 37, and new Claims 42-46.

Claims 25-27, 32-35, and 37-46 are pending for examination.

Applicants thank the Examiner for her careful review of the instant application and for withdrawing the rejection of Claims 22-41 under 35 U.S.C. § 112, first paragraph, for lack of enablement regarding the lack of an adequate biological deposit, and Claims 22-41 under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants acknowledge the Examiner's grant of a priority date of 12/1/1999. Claims 22-29, 35 and 37-41 stand rejected as unpatentable under 35 U.S.C. §112, first paragraph, for lack of enablement, and Claims 22-27, 35 and 37-41 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement. The Examiner has also maintained the rejection of Claims 22-29, 33-35, and 37-41 under 35 U.S.C. § 102(b). Applicants acknowledge that Claim 32 is objected to as being dependent upon a rejected claim, but would be allowable if rewritten in independent form. For the reasons set forth below, Applicants respectfully traverse.

**Rejections under 35 U.S.C. § 112, first paragraph – Enablement**

The PTO has rejected Claims 22-29, 35, and 37-41 under 35 U.S.C. § 112, first paragraph, because in its view, while the specification is enabling for nucleic acids of SEQ ID NO: 1 or fragments of such that are usable as hybridization probes, it is not enabling for degenerate variants of SEQ ID NO: 1, for nucleic acids with 80, 85, 90 or 95% identity to SEQ ID NO: 1, for nucleic acids with 80, 85, 90 or 95% identity to a sequences which encodes a protein of SEQ ID NO: 2, or for nucleic acids which hybridize to any of the above. Applicants respectfully disagree.

*PTO has Initial Burden to Establish a Reasonable Basis to Question the Enablement Provided*

In order to make an enablement rejection, the PTO has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See* M.P.E.P. § 2164.04 (8th ed. May 2004). A specification teaching how to make and use the claimed subject matter must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. *Id.* It is incumbent for the PTO "to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *Id.* (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (CCPA 1971). This can be done "by

making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact." *Id.*

*Determination of Enablement Based on Evidence as a Whole*

Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on the applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See* M.P.E.P. § 2164.05 (8th ed. May 2004). "The evidence provided by applicant **need not be conclusive but merely convincing** to one skilled in the art." *Id.* (bold emphasis added, underline in original). "A declaration or affidavit is, itself, evidence that must be considered." *Id.* (emphasis in original).

The examiner must then "weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled." *Id.* "The examiner should **never** make the determination based on personal opinion. The determination should always be based on the weight of all the evidence." *Id.* (emphasis in original).

*Weighing All the Evidence, the Pending Claims are Enabled*

Applicants note that the PTO has acknowledged that the specification is "enabling for the nucleic acids of SEQ ID NO: 1 or fragments of such that are usable as hybridization probes" and that the specification "enables the use of PRO1800 nucleic acids or fragments thereof for diagnosis of lung squamous cell carcinoma." (Office Action at 3, 7). In the previous Office Action, a position relied on in the present Office Action, the PTO stated that "nucleic acids that are claimed by what they encode, rather than the structure of the nucleic acid itself, are not enabled in a manner commensurate with the claims." (5/13/2004 Office Action at 4).

Claims 25-27 and 35 have been amended to delete elements (a) and (b) which defined the claimed nucleic acids in part by the sequence of the polypeptide they encoded, rather than the sequence of the nucleic acid itself. In addition, Applicants have amended Claims 22-26 to require that the claimed nucleic acids hybridize to the complement of a nucleic acid of SEQ ID

NO: 1 under the specified stringent conditions. It is well known in the art how to make sequences which are homologous to a disclosed sequence such as SEQ ID NO: 1. It is also well known in the art how to determine whether a nucleic acid of a given sequence will hybridize under the specified conditions to SEQ ID NO: 1 or its complement. Applicants submit that there is no reason to distinguish between sequences which are identical to SEQ ID NO: 1, and those that are homologous, when determining if the sequences are enabled as hybridization probes. It is well known in the art that a sequence need not be the exact complement of the target sequence to hybridize, even under stringent conditions. As a result, Applicants submit that each of the claimed nucleic acids is enabled as a hybridization probe of SEQ ID NO: 1.

In the previous Office Action, the PTO stated that claims directed to nucleic acids which hybridize, even under stringent conditions, are not commensurate in scope with the enablement provided in the specification. (5/13/2004 Office Action at 5). The PTO argued that giving the claims their broadest reasonable interpretation, the language "reads on an infinite number of possible DNA sequences for which there is not sufficient enablement." (5/13/2004 Office Action at 5). The PTO argued that "[t]he examples provided in the specification do not provide a representative number of different DNA sequences that would enable a representative number of the above discussed DNA sequences with assurances that they possess or encode proteins having the desired activity, or alternatively can be used as probes or primers for the purpose of amplifying or detecting the PRO1800 gene." (5/13/2004 Office Action at 5).

Applicants submit that the amendments to the claims which have deleted elements (a) and (b), significantly reduce the number of possible nucleic acid sequences within the scope of the claims. The claimed nucleic acids are no longer defined by what they encode. Given the disclosure of SEQ ID NO: 1, it would be well within the skill of those in the art to determine which sequences would hybridize to the nucleic acid sequence of SEQ ID NO:1 or the complement thereof; the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:1 or the complement thereof; or the full-length coding sequence of the cDNA deposited under ATCC accession number 203538 or the complement thereof. This is particularly true in light of the amendment to the claims specifying the hybridization conditions.

By amending the claims so that the claimed nucleic acids are not defined by the sequence of the polypeptide they encode, Applicants have also rendered moot the question of whether gene amplification leads to increased expression of the encoded protein. While Applicants maintain

that generally that is the case, this issue does not need to be resolved to establish the enablement of the claimed nucleic acids.

Given the above amendments and arguments, Applicants submit that the pending claims are enabled, and request that the PTO reconsider and withdraw its rejection of the claims under 35 U.S.C. § 112, first paragraph.

**Rejections under 35 U.S.C. § 112, first paragraph – Written Description**

The PTO has rejected Claims 22-27, 35 and 37-41 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. The PTO maintains this rejection for the reasons stated in the previous Office Action. The PTO argues that "[t]he claims do not require that the claimed polynucleotide encode a particular protein, nor that any protein encoded thereby possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature" and therefore the claims are drawn to a genus of polynucleotides that are defined only by sequence identity. (Office Action at 8). Applicants respectfully disagree.

*The Legal Standard for Written Description*

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

*The Current Invention is Adequately Described*

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

Applicants initially note that Claim 27 does not include any percent sequence identity language, and therefore Applicants respectfully submit that a rejection based on the argument that the claims are drawn to a large genus defined only by sequence identity clearly do not apply to this claim.

The subject matter of the pending claims concerns nucleic acids having 95% or 99% sequence identity to the nucleic acid sequence of SEQ ID NO:1, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:1, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203538, with the functional recitation as amended: "wherein said isolated nucleic acid hybridizes to the complement of a nucleic acid of SEQ ID NO: 1" under the specified conditions. Other claimed nucleic acids are those which hybridize to the nucleic acid sequence of SEQ ID NO:1, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:1, the full-length coding sequence of the cDNA deposited under ATCC accession number 203538, or the complements thereof, under the specified stringent conditions. As mentioned above, the deletion of elements (a) and (b) from the claims significantly narrows the scope of the claimed invention.

In *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), the Court held that functional descriptions of genetic material may satisfy the written description requirement. In so holding, the Court gave judicial notice to the USPTO's Manual of Patent Examining Procedure, which provides that the written description requirement may be satisfied when the disclosure provides sufficiently detailed identifying characteristics, such as "complete or partial structure,

other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Id.* at 964, quoting 66 Fed. Reg. at 1106 (emphasis in original). In *Enzo*, the Court found describing nucleic acids based on their ability to hybridize to another nucleic acid sequence which was adequately described may be an adequate description of the nucleic acid. This is because the hybridization function of a nucleic acid is dependent on the sequences of the nucleic acid – a disclosed function which is coupled with a known correlation between function and structure. The Court favorably discussed the PTO's example wherein "genus claims to nucleic acids based on their hybridization properties...may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Id.* at 967 (citing *Application of [Written Description] Guidelines*, Example 9) (emphasis added).

Applicants submit that the stringent hybridization conditions specified in the pending claims, alone or in combination with the recited percent sequence identity, result in all species within the genus being structurally similar. As the *Enzo* Court noted, Examples 9 and 10 of the Application of Written Description Guidelines (hereinafter "Guidelines") make clear that specifying hybridization under highly stringent conditions yields "structurally similar DNAs." Guidelines, Example 9 at page 36. The analysis of a genus claim in Example 10 of the Guidelines states:

> [T]urning to the genus analysis, the art indicates that *there is no substantial variation within the [claimed] genus because of the stringency of hybridization conditions which yields structurally similar molecules*. The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Guidelines, Example 10 at page 39 (emphasis added).

Given the level of skill in the art, specifying highly stringent conditions leads to "no substantial variation within the [claimed] genus," and therefore a skilled artisan would recognize that the Applicants were in possession of the necessary common attributes or features of the genus. This is contrary to the PTO's argument the claimed sequences do not possess any particular conserved structure, or other disclosed distinguishing feature. The common element or

attribute of the claimed genus is that species of the genus are structurally related to SEQ ID NO:1, such that they hybridize to SEQ ID NO:1 or the related sequences under the specified high stringency conditions recited in the claims.

The present situation is not analogous to *Fiddes v. Baird*, 30 U.S.P.Q.2d 1481, cited by the PTO. Unlike *Fiddes*, where arguably the structure of other mammalian sequences could not be conceived based on a single species of the genus, here the skill in the art is such that the sequence of nucleic acids which hybridize to SEQ ID NO: 1 under the conditions specified can be conceived. Here, the claimed genus is defined by its structure – members of the genus hybridize under the specified conditions to the specified sequences, each of which are adequately described in the specification.

Applicants note that Claims 22-27, 35 and 37-41 are analogous to the claims discussed in Example 9 and Example 14 of the written description training materials. In Example 9, the written description requirement was found to be satisfied with respect to claims reciting polynucleotides which hybridize to particular nucleic acids under stringent conditions even though the specification did not contain a working example clearly demonstrating the existence of homologous nucleic acids. In Example 14 of the written description training materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity even though the applicant had not made any variants.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No. 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502, which are attached hereto as Exhibits 1-6.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims by reducing the nucleic acid of SEQ ID NO: 1 to practice, and by specifying the high stringency conditions under which hybridization occurs. Together, this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the

members of the genus." Thus, Applicants respectfully request that the PTO reconsider and withdraw its rejection of the pending claims under 35 U.S.C. § 112, first paragraph.

**Rejections under 35 U.S.C. § 102(b) – Anticipation**

The PTO has not expressly withdrawn or maintained its previous rejection of Claims 35 and 37 under 35 U.S.C. § 102(b) as being anticipated by F. Gabrielli et al., Eur. J. Biochem 232:473, 1995 (hereinafter Gabrielli). In the previous Office Action, the PTO asserted that Gabrielli disclosed a protein which is 62% identical to SEQ ID NO: 2. The PTO asserted that the nucleic acid encoding the protein would have sufficient regions of identity to SEQ ID NO: 1 so as to hybridize to it, even under stringent conditions. Applicants submit that Gabrielli does not anticipate Claim 35 and 37 because it fails to teach each and every element of the claimed invention.

Under 35 U.S.C. §102(b), "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). As amended, Claim 35 requires that the claimed nucleic acid be at least about 200 nucleotides in length and hybridize under the stringent conditions specified. Claim 37 requires that the claimed isolated nucleic acid be at least about 250 nucleotides in length. Given the low degree of homology between the sequence disclosed in the cited art and SEQ ID NO: 1, Applicants believe that Gabrielli does not disclose a nucleic acid sequence that is at least about 200 (or 250) nucleotides in length which hybridizes to SEQ ID NO: 1 or any of the related sequences identified in Claims 35 and 37 under stringent conditions. For this reason, applicants request that the PTO reconsider and withdraw the anticipation rejection of Claims 35 and 37 under 35 U.S.C. §102(b) based on Gabrielli.

The PTO has maintained its rejection of Claims 22-29, 33-35 and 37-41 under 35 U.S.C. § 102(b) as being anticipated by DE 198 18 620 (Rosenthal et al.). The PTO asserts that Rosenthal discloses a nucleic acid, SEQ ID NO: 10, which is 100% identical to SEQ ID NO: 1 of the instant application, with the exception of nine nucleotides at the amino terminus of SEQ ID NO: 1. The PTO also asserts that Rosenthal discloses vectors, host cells, and fusion constructs, and that numerous disclosed vectors are specific to *E. coli*. The PTO states that the instant

application has a priority date of 5/25/2001, and therefore Applicants argument that Rosenthal is not available as prior art under 35 U.S.C. § 102(b) is not persuasive.

To anticipate under 35 U.S.C. § 102(b), the invention must be patented or described in a printed publication "more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). On page 2 of the instant Office Action, under the heading "***Priority Determination***," the PTO states that priority for the instant application is set at 12/1/99. It is not clear to Applicants why the PTO later states on pages 8 and 9 of the Office Action that the effective priority date of the application is 5/25/2001. In the previous Office Action, the PTO stated that the priority was set at 5/25/2001, with possible priority to 12/1/99, pending review of PCT application PCT/US99/28634 for support for the results of Example 16 found in the instant application. Applicants have provided the PTO with a copy of the relevant pages of PCT/US99/28634 which disclose the results of Example 16, and the PTO acknowledged on page 2 of the instant Office Action that priority to 12/1/99 is appropriate. Therefore, Applicants submit that they have established priority to at least 12/1/1999.

Applicants submit that Rosenthal does not anticipate claims 22-27, 33-35 and 37-41 because it was not published more than one year prior to the date of the instant application for patent in the United States. As discussed previously, the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 09/866034 filed May 25,2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US99/28634 filed December 1, 1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/112851 filed December 16, 1998. SEQ ID NOs: 1 and 2 were first disclosed in Figures 1 and 2 of US Provisional Application 60/112851 filed December 16, 1998. Rosenthal was published October 28, 1999. Thus, Rosenthal was not published more than one year prior to the filing of either PCT Application PCT/US99/28634, filed December 1, 1999, or US Provisional Application 60/112851, filed December 16, 1998. The instant application claims priority to both, the PTO has acknowledged priority to 12/1/99, and therefore Rosenthal cannot be cited as prior art against the instant application under 35 U.S.C. § 102(b). For this reason, Applicants request that the PTO reconsider and withdraw the rejection under 35 U.S.C. §102(b) based on Rosenthal.

The PTO has also maintained its rejection of Claims 22-29, 33-35 and 37-41 under 35 U.S.C. § 102(b) as being anticipated by Genebank locus AF044127 disclosed May 27, 1999. The

PTO asserts that the clone is identical to nucleotides 11-terminus of SEQ ID NO: 1 of the instant application and discloses an expression vector and *E. coli* as a host cell. As with Rosenthal, Applicants submit that Genebank locus AF044127 is not a 35 U.S.C. § 102(b) reference because it was not published more than a year before the priority date of the instant application.

Genebank locus AF044127 was disclosed May 27, 1999. Thus, Genebank locus AF044127 was not published more than one year prior to the filing of either PCT Application PCT/US99/28634, filed December 1, 1999, or US Provisional Application 60/112851, filed December 16, 1998. The instant application claims priority to both, the PTO has acknowledged priority to 12/1/99, and therefore Genebank locus AF044127 cannot be cited as prior art against the instant application under 35 U.S.C. § 102(b). For these reasons, applicants request that the PTO reconsider and withdraw the rejection under 35 U.S.C. §102(b) based on Genebank locus AF044127.

## CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any necessary fees, including any fees for any extensions of time, to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 31, 2005

By: _____

AnneMarie Kaiser
Registration No. 37,649
Attorney of Record
Customer No. 30,313
(619) 235-8550

1329513_1
031005